Assessment of cardiovascular disease risk: a 2023 update

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Purpose of review
The aim of this study was to highlight the current best practice for atherosclerotic cardiovascular disease (CVD) risk evaluation, including selective use of adjunctive tools for risk stratification [e.g. coronary artery calcium (CAC) scoring] and risk enhancement [e.g. lipoprotein(a) [Lp(a)], polygenic risk scoring (PRS)].

Recent findings
New studies have evaluated the efficacy of various risk assessment tools. These studies demonstrate the role of Lp(a) as a risk-enhancing factor ready for more widespread use. CAC is the gold standard method of assessing subclinical atherosclerosis, enabling true risk stratification of patients, and informing net benefit assessment for initiating or titrating lipid-lowering therapy (LLT).

Summary
Lp(a) concentration and CAC scoring, apart from the traditional risk factors, add the most value to the current CVD risk assessment approaches of all available tools, especially in terms of guiding LLT. In addition to new integrative tools such as the MESA CHD Risk Score and Coronary Age calculator, the future of risk assessment may include PRS and more advanced imaging techniques for atherosclerosis burden. Soon, polygenic risk scoring may be used to identify the age at which to begin CAC scoring, with CAC scores guiding preventive strategies.

Keywords
atherosclerotic cardiovascular disease, assessment, cardiovascular disease, coronary artery calcium, lipoprotein(a)

INTRODUCTION

Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality worldwide, with atherosclerotic cardiovascular disease (ASCVD) being the dominant cause of total CVD mortality [1]. According to NHANES data from 2015 to 2018, the prevalence of CVD, excluding hypertension, is 9.3% in the USA [2]. The current global prevalence of CVD has nearly doubled in the last two decades [3], and current data portend further increases through 2024 [4].

Some factors contributing to this projected increased prevalence are the increasing age of the population and the significantly increased prevalence of metabolic syndrome (MetS) in U.S. adults [5]. Accordingly, it is imperative to conduct an ASCVD risk assessment, especially in patients with MetS (e.g. dyslipidaemia), as risk with MetS is variable and not well captured with traditional risk factors [6,7].

There have been several advances to ASCVD risk assessment [8]. Emphasis has migrated from isolated appraisal of ASCVD risk factors towards a more holistic estimation of risk, including assessment of subclinical atherosclerosis, genetic risk and other less-recognized ASCVD risk factors [9]. This review emphasizes current gold-standard methods of clinically appraising ASCVD risk while discussing contemporaneous risk stratification tools and risk-enhancing factors, which should also be considered in clinical assessment.

TRADITIONAL RISK CALCULATORS

Traditional risk calculators are risk assessment tools, which operationalize known ASCVD risk factors

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KEY POINTS

- The PCE are the gold standard tool for primary ASCVD risk assessment in the USA.
- CAC scoring enhances risk prediction and is a stronger predictor of ASCVD risk than the PCE. CAC affords true risk stratification.
- Advanced lipid testing is recommended for select patients, and Lp(a) is a key serum marker of residual cardiovascular risk. Lp(a) is the ideal risk-enhancing factor.
- Integrated risk tools are hybrid risk calculators, which offer a unique opportunity to combine multiple risk elements in a single calculator, improving efficiency and risk communication in clinical risk assessment.

into an equation, deriving risk of an ASCVD event over a defined period of follow-up time [10].

Pooled cohort equations

The Pooled Cohort Equations (PCE) are a traditional risk calculator developed in 2013 by the Working Group of the American College of Cardiology and American Heart Association (ACC/AHA) [10] and estimates the 10-year risk of an incident hard ASCVD event [e.g. nonfatal myocardial infarction (MI), stroke death, CVD death] for non-Hispanic African–American and non-Hispanic White adults aged 40–79 years [11,12]. In addition, the extended ACC/AHA tools estimate lifetime risk of an incident hard ASCVD event in non-Hispanic AA and non-Hispanic White adults aged 20–59 years. The PCE are derived from the data of two generations of Framingham data, as well as three other large U.S. cohort studies (i.e. ARIC, Cardiovascular Health and CARDIA studies [11]). The PCE are currently endorsed by the ACC/CHA for the primary clinical risk assessment of ASCVD [10]. For racial/ethnic groups outside of the non-Hispanic African–American and non-Hispanic white groups, it is recommended that the equation for non-Hispanic white adults be used and that results be cautiously interpreted [10].

The PCE delegates risk into one of four absolute risk categories: low (<5%), borderline (5 to <7.5%), intermediate (7.5 to <20%) and high (≥20%). These values represent the risk of an incident ASCVD event within the next 10 years [10]. These scores are used to guide preventive efforts, which range from discussion of lifestyle change to initiation of high-intensity statin therapy [12].

Although the PCE are the current gold standard for primary risk assessment according to the ACC/AHA [10], they carry notable limitations. The PCE have limited applicability beyond the stringent racial/ethnic categories indicated in their validation [9]. In addition, the PCE have been demonstrated to overestimate ASCVD risk by approximately 20% across all risk groups [13] while underestimating risk in specific youth with high-risk conditions (e.g. monogenic familial hypercholesterolemia) [8,14]. Finally, the PCE are predicated upon the data from old cohort studies, prompting re-validation using contemporaneous data [15]. Finally, the PCE were derived from large cohort data [11] but are used to appraise risk at the individual level.

Systemic COronary risk evaluation 2 (SCORE 2) and SCORE 2-old persons (SCORE 2-OP)

The Systemic COronary Risk Evaluation 2 (SCORE 2) is a traditional risk calculator endorsed by the European Society of Cardiology (ESC) since its development in 2021. It is a country and sex-specific calculator, which estimates the 10-year risk of an incident CVD event (i.e. CVD mortality, MI, stroke), and it is indicated for the primary risk assessment in European adults aged 40–69 years with no known CVD or diabetes [16]. SCORE 2 is based upon the original traditional risk calculator, SCORE, but demonstrates more inclusive study endpoints (e.g. 10-year incident fatal and nonfatal CVD event) and an expanded age range (i.e. 40–69 years), includes diabetes mellitus as a risk factor, and is derived from the data of 45 diverse cohorts across 13 European countries [17]. SCORE2 employs a recalibrated risk estimation, wherein the β-coefficients for risk factors are identical to those in SCORE, but the models are recalibrated to represent the population-based CVD incidences and mean risk factor levels in four different risk regions within Europe [17]. Application to external validation cohorts demonstrates C-indices ranging from 0.67 to 0.81 [17].

SCORE 2-Old Persons (SCORE 2-OP) is similar to SCORE 2 but differs in its indicated population – European adults aged at least 70 years with no known incident CVD (i.e. CVD mortality, MI, stroke). This tool estimates 5 and 10-year risk of an incident CVD event across four geographic risk regions; geographic risk regions are determined by CVD mortality rates for a given European country. Application to external validation cohorts demonstrates C-indices ranging from 0.63 to 0.67 [18]. Traditional risk calculators are classic risk assessment tools (Table 1).

IMAGING

Imaging is an important tool used to quantify subclinical vascular disease (e.g. calcified and

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Table 1. Traditional risk calculators

Traditional risk calculator	Indicated population	Indicated age range	Endpoint	Strengths	Limitations
PCE [8–12]	Non-Hispanic AA and White U.S. adults with known incident CVD	40–79 y *20–59 y	10 y risk of incident hard ASCVD event (i.e. nonfatal MI, stroke death, CHD death) *Lifetime risk of hard ASCVD event	Endorsed by the ACC/AHA; derived from data of 4 larger U.S. cohort studies	Stringent racial/ethnic categories; overestimation of ASCVD risk; underestimation of risk in high-risk youth; predicated upon outdated data
SCORE 2 [13,14]	European adults with no known incident CVD	40–69 y	10-year risk of incident CVD event (i.e. CVD mortality, MI, stroke)	Endorsed by the ESC; derived from data of 45 diverse cohorts across 13 European countries; C-indices 0.67–0.81; use of geographic risk regions	Limited age range
SCORE 2-OP [15]	European adults with no known incident CVD	≥70 y	5-year risk of incident CVD event (i.e., CVD mortality, MI, stroke) 10 y risk of incident CVD event	Expanded age range; C-indices 0.63–0.67; use of geographic risk regions	Paucity of longitudinal data evaluating efficacy

AA, African–American; ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; CVD, cardiovascular disease; MI, myocardial infarction; PCE, Pooled Cohort Equations; SCORE 2, Systemic COronary Risk Evaluation 2; SCORE 2-OP, Systemic COronary Risk Evaluation 2-Old Persons.

noncalcified atherosclerotic plaque) contributing to CVD risk. It can be used for risk stratification, especially when decision for pharmacotherapy initiation or intensity is unclear [10–12]. Risk stratification is defined by the ability to move patients both up and down the risk spectrum based on the results of a test.

Coronary artery calcium scoring

Coronary artery calcium (CAC) scoring employs the use of noncontrast computed tomography to assess subclinical atherosclerosis though the quantification of coronary artery calcified plaque burden [19]. CAC scoring is widely accessible, cheap (~$75–150) and rapid (10–15 min). The ACC/AHA guidelines indicate the use of CAC in the arbitration of initiating statin therapy in patients for whom the indication is unclear [12]. CAC imaging can produce absolute scores as well, as it can produce age, sex and race-specific score percentiles. Scores and percentiles predict absolute (5–10 year) cardiovascular risk and lifetime risk trajectory, respectively [20].

CAC scoring is the single best predictor of CHD and CVD events [21–23] and exhibits the strongest prognostic value for the prediction of cause-specific ASCVD mortality [20]. It has been demonstrated to effectively stratify cardiovascular risk across ethnic groups [20]. CAC at least 1000 portends very high ASCVD risk, which would benefit from aggressive therapeutic intervention [e.g. high-intensity statin therapy or ezetimibe/proprotein convertase subtilisin/kexin type 9 inhibitor (PCSK9i) if low-density lipoprotein cholesterol (LDL-C) <70 mg/dl] [24,25▪▪]. Meanwhile, CAC = 0 is a negative risk factor, which predicts low and stable rates of CVD mortality for 12 years [26].

Important limitations to CAC scoring relate to exposure to radiation and the potential false assurance of CAC = 0. First, CAC measures calcified plaque only – thus, not directly representing the noncalcified plaque that may be present in the small proportion of incident cardiovascular events in those with CAC = 0. However, the burden of noncalcified plaque in those with CAC = 0 is not high (i.e. average plaque volume 30.4 μl) (Fig. 1), supporting the use of CAC as a general measure of total plaque burden [27▪▪]. Second, CAC = 0 is a negative risk factor for short-term prognostication, though it is limited in prognosticating lifetime risk without appropriate rescanning, as up to one-third of incident lifetime CVD events occur in patients with CAC = 0 [28]. Indeed, all patients start with a CAC = 0. Reliance on a single CAC score at early middle-age may lead clinicians to believe that atherosclerotic events occur in patients with a concurrent CAC = 0. Thus, this obfuscation can be addressed with appropriate re-testing of patients with initial CAC = 0. Data from a 2021 study suggests a rescanning of CAC within 3–7 years for

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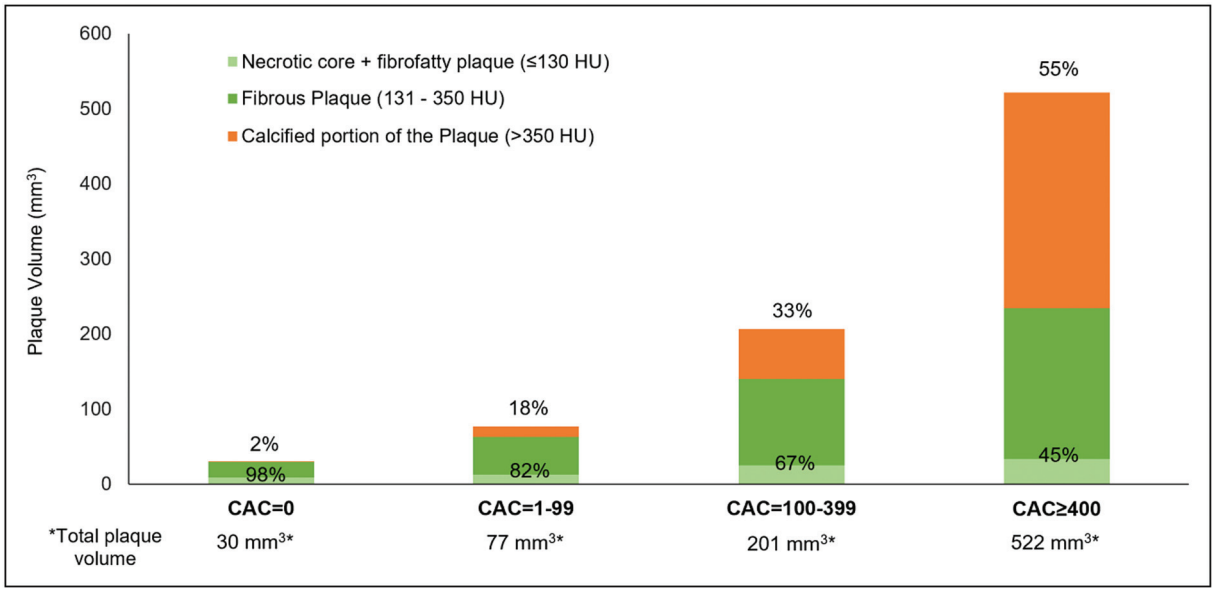

FIGURE 1. Burden of noncalcified plaques according to CAC score. Adapted from [27▪▪].

individuals with an initial CAC = 0, given a prevalence of CAC more than 0 of 46% within 10 years upon rescan [29], a recommendation endorsed by the Endocrine Society and National Lipid Association (NLA) [30,31].

Carotid ultrasound

Carotid ultrasound imaging largely falls into one of two techniques, carotid intima-media thickness (CIMT) and imaging of carotid plaque. CIMT estimates risk of CVD by intima-media thickness of the carotids [32]. For every 0.1 mm increase in CIMT, there is an associated 10–15% increased risk of MI [33]. A 2020 meta-analysis yielded data demonstrating the protective role of CIMT reduction, noting that a 10 μm/year reduction in CIMT progression was associated with a decreased risk of CVD [relative risk (RR) = 0.91; 95% confidence interval (95% CI) 0.87–0.94]. Estimated reductions of CIMT progression by 10; 20; 30; or 40 μm/year would result in reductions in CVD risk (RR = 0.84; 95% CI 0.75–0.93; 0.76; 95% CI 0.67–0.85; 0.69; 95% CI 0.59–0.79; 0.63; 95% CI 0.52–0.74, respectively) [34]. However, measuring CIMT is a Class III recommendation according to the ACC/AHA Guidelines on Assessment of CV risk [11], largely due to its cost, concerns with reproducibility and limited clinically significant prognostication beyond that afforded with traditional risk factors [35–37]. In the USA, carotid ultrasound is not recommended as a screening tool. CAC is preferred as the first imaging test when risk stratification is desired [11]. However, in areas where CAC is not widely available, including some parts of Europe and South America, carotid plaque can be used as an alternative to CAC.

Coronary computed tomography angiography

Coronary computed tomography angiography (CCTA) lacks formal substantiation from guidelines for use in primary risk assessment of CVD [10]. CCTA assesses the degree of coronary atherosclerosis – especially noncalcified plaque burden – and the degree of coronary stenosis in asymptomatic patients [32,38]. A 2022 study using data from the Miami Heart study used CCTA to demonstrate that 49% of asymptomatic patients with a CAC = 0 had some degree of coronary plaque; 6% had stenosis at least 50%; and 7% had plaques with at least one high-risk feature (i.e. positive remodelling, low attenuation plaque, spotty calcifications, napkin ring) [39]. A 2021 study demonstrated a prevalence of 9.2% for CCTA-verified atherosclerosis in patients with a CAC = 0 and intermediate 10-year risk of incident CHD [40]. The unique ability of CCTA to identify noncalcified plaque positions it as a potentially valuable tool in clinical risk assessment, as a 2020 study demonstrates plaque burden, rather than the degree of stenosis, is the major predictor of risk for CVD events and CVD death [41].

CCTA has a proposed utility as a noninvasive means of stratifying risk in asymptomatic patients with familial hypercholesterolemia. In a 2015

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Japanese study, CCTA identified coronary plaque burden was associated with future coronary events in those with heterozygous familial hypercholesterolemia (HeFH) [42]. Similarly, CCTA may have a role in stratifying risk for those with a family history of premature CVD. A 2018 pilot study identified obstructive CHD by CCTA in 18% of participants who were asymptomatic but had a sibling with a young MI (i.e. age $\leq$55 years) [43].

ADVANCED LIPID TESTING

Advanced lipid testing is not the gold standard when assessing ASCVD risk, as LDL-C and non-HDL-C provide sufficient information for risk assessment in most patients. However, it can provide invaluable information, particularly as risk-enhancing factors. Risk-enhancing factors help identify unexpectedly high-risk patients, but do not necessarily provide reassurance when values are low. Advanced lipids tests can serve as risk-enhancing factors especially in particular high-risk youth (e.g. known or suspected HeFH), which can be utilized to guide and enhance preventive therapies [44]. The NLA proposes the utility of advanced lipid testing to gauge the adequacy of treatment in select patients (i.e. those at high ASCVD risk with LDL-C $<$70 mg/dl) with the most commonly used assays being apoB and LDL-P [45].

Apolipoprotein B

Apolipoprotein B (apoB) should be measured if serum triglycerides at least 200 mg/dl. ApoB at least 130 mg/dl is a risk-enhancing factor which favours the initiation of statin therapy [10,46]. ApoB demonstrates a better discriminatory power for prevalent CVD than nonhigh-density lipoprotein cholesterol (HDL-C) and LDL-C [ROC 0.60 ($P<0.001$); ROC 0.57 ($P=0.001$); ROC 0.54 ($P=0.108$), respectively] [47]. However, routine assessment of apoB for the purposes of risk stratification is controversial, as it may not add risk prediction beyond routine lipoprotein cholesterol concentration measurement, even in patients with obesity and insulin resistance syndromes [48].

LDL particle number

LDL particle (LDL-P) number is an alternative to LDL-C and represents the concentration of LDL particles/litre of plasma volume [49]. It has a proposed utility in patients with low HDL-C, hypertriglyceridemia, MetS and diabetes mellitus for whom there is a greater likelihood of discordance between concentrations of LDL-C and LDL-P [50–52]. LDL-P has been demonstrated to be a better predictor of CVD risk than LDL-C [53].

Lipoprotein A

Lipoprotein (Lp(a)) is an independent risk factor for premature CHD. Elevated Lp(a) portends risk comparable to total cholestrole (TC) at least 240 mg/dl or HDL-C 35 mg/dl or less [46,54,55]. Elevated Lp(a) is useful in stratifying risk after initiation of statin therapy [56]. Molar concentrations of Lp(a) are stable regardless of statin use, arguing against repeat measurements [57]. This is because Lp(a) is relatively stable throughout an individual's lifetime, irrespective of lifestyle [58], positioning it a distinct mechanism from other lipid measures, which are largely variations of the HDL-C and LDL-C (e.g. LDL-C, non-HDL-C, ApoB, LDL-P). Elevated Lp(a) is predictive of 15-year CVD outcomes and enhances CVD risk estimation [59]. ALthough the ESC recommends Lp(a) measurement in all adults once in a lifetime [60▪], the ACC/AHA 2018 Guideline on the Management of Blood Cholesterol does not endorse routine measurement of Lp(a). However, if these data are available to the clinician and Lp(a) at least 50 mg/dl or at least 125 nmol/l, it should be considered a risk-enhancing factor favouring moderate-intensity statin therapy for patients aged 40–75 years with intermediate 10-year ASCVD risk and LDL-C between 70 and 189 mg/dl [12]. Per these guidelines, Lp(a) measurement may aid risk discussion of initiating statin therapy for patients aged 40–75 years with borderline and intermediate 10-year ASCVD risk and LDL-C between 70 and 189 mg/dl [12].

The NLA notes that the measurement of Lp(a) may be valuable in patients with a strong family history of ASCVD, in patients who do not exhibit an adequate response to statin therapy, and for those with an ASCVD event while on evidence-based LLT [61]. However, multiple countries now recommend one-time measurement of Lp(a) for everyone [62,63].

POLYGENIC RISK SCORING

PRS is an age-independent tool which estimates the risk of developing complex traits (e.g. CVD) based on an individual's genotype. Individual risks conferred by genetic variants previously identified to confer risk of the complex trait are operationalized into an equation, which then collectively appraises risk of the complex trait [64]. The associations between various genotypic profiles and complex traits are based on data from genome-wide association studies (GWAS) and are used to personalize risk assessment [65]. Age-independence positions PRS as a useful clinical tool, especially for cohorts with

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predetermined risk of CAD, serving to guide the implementation of preventive strategies to mitigate future risk [66–68].

Currently, there is little indication for its routine use in the clinical assessment of ASCVD risk, and PRS is not yet considered a risk-enhancing factor for use in the adjudication of benefit from statin therapy, according to the 2018 ACC/AHA Guidelines for Blood Cholesterol Management [12]. The NLA endorses the consideration of PRS only if PRS will provide data, which modifies prognosis or treatment in select patients with severe dyslipidaemia [69]. A 2022 cohort study demonstrated that PRS accounted for 30% of MI risk in younger adults (i.e. age <50 years) and reclassified risk to favour initiation of statin therapy in those originally considered borderline or intermediate clinical risk for CAD [70▪]. Major challenges to the incorporation of PRS to ASCVD risk assessment include the utilization of only common variants in current models, limiting the power of these models, high cost, and low accessibility [71]. PRS has a projected future utility, given its static appraisal of ASCVD risk, particularly in younger patients in whom its association with risk appears more pronounced [9].

INTEGRATED RISK TOOLS

Integrated risk tools (IRT) are risk stratification tools which combine variables from varying risk assessment classes (e.g. traditional risk calculators, imaging, genetic scoring) into one risk stratification tool [9]. The MESA CHD Risk Score is a notable IRT. However, others exist in varying combinatorial pairings. Currently, IRT lack specific guideline endorsement in clinical risk assessment, although they are likely the way of the future [11].

MESA CHD risk score

The MESA CHD Risk Score ('MESA') is a risk estimation tool comparable to the PCE in the traditional risk factors operationalized but additionally includes CAC score, family history of MI, and whether the patient is currently on a lipid-lowering therapy (LLT) in its holistic estimation of CHD risk. This tool estimates the 10-year risk of incident CHD (i.e. coronary death, MI, adjudicated angina with revascularization). Generally, multiplication of MESA CHD risk by 1.5 gives a risk more equivalent to the ASCVD risk output of the PCE. Inclusion of CAC in MESA yielded a greater C-statistic (0.80 vs. 0.75, $P < 0.0001$) and discrimination between events and nonevents [72].

This tool is derived from Multi-Ethnic Study of Atherosclerosis (MESA) data [19]; thus, it is indicated for multiple racial/ethnic groups, circumventing a major limitation of the PCE. In addition, its indicated age range (i.e. 45–84 years) [72] is more inclusive for older age groups than the PCE. When considering the entire population, discrimination with the MESA with CAC was comparable with the PCE for risk of CHD (C-statistics 0.80 and 0.79, respectively) and CVD deaths (C-statistics 0.77 and 0.78, respectively) over a mean 12 years of follow up [73]. Notably, MESA with CAC demonstrated greatest discrimination of CHD risk for patients with 5–20% estimated risk (C-statistic 0.71) [73]. Further, addition of CAC to MESA demonstrates modestly enhanced risk discrimination among low and high-estimated risk groups [73]. MESA also demonstrates enhanced prediction of incident cardiovascular events than the PCE (C-statistics 0.770 vs. 0.653, respectively [74]. The MESA tool can be converted into a 'coronary age', a single number that converts 10-year CHD risk into the age-equivalent of that risk (i.e. 'you have the coronary arteries of a 75 year old') [75].

Others

PCE-polygenic risk score (PRS) IRT exist, with one demonstrating enhanced predictive performance over the PCE, alone, and extended racial/ethnic indications. This IRT demonstrated net reclassification improvement (NRI) across multiple ethnic groups not represented in the PCE, including South Asian (NRI = 8.7%) and Hispanic (NRI = 7.5%) ethnic groups [76]. Another PCE-PRS IRT also demonstrated enhanced predictive performance over the PCE (NRI = 5.9%), with the greatest predictive performance in middle-aged men aged 40–54 years (NRI = 15.4%) [77].

PCE-CAC IRT represents another combinatorial pairing of IRT. CAC has been particularly effective in reclassifying risk in patients with intermediate risk as determined by the PCE [9]. One IRT added CAC scoring to the PCE, yielding improved C-statistics for CHD (+0.03) and CVD (+0.02) deaths [73].

CAC-PRS IRTs are sparse; the few studies which do investigate the utility of these IRT are more likely to evaluate the efficacy of PRS in terms of concordance with CAC scoring [66,78▪▪,79]. In CARDIA, higher PRS values were associated with greater increases in CAC over time, though this finding was not replicated in the Framingham cohort [76]. Neither CAC scoring nor PRS is bound by restrictions for age or race, as with the PCE; however, neither is first-line in the clinical risk assessment of ASCVD and, thus, lack formal guidelines for their primary use.

To date, there are no known studies explicating the development of a CAC-PCE-PRS IRT in the

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clinical appraisal of ASCVD risk. IRT are diverse (Table 2).

OTHER RISK-ENHANCING FACTORS

Risk-enhancing factors are features which increase risk when present but do not act as negative risk factors when absent; they are particularly useful in deciding LLT in individuals with intermediate or borderline risk [80]. Notable risk-enhancing factors include dyslipidaemia, elevated TC in the elderly, family history of premature ASCVD, MetS, particular advanced lipid profiles [e.g. elevated Lp(a), elevated ApoB), chronic inflammatory conditions (e.g. periodontitis, rheumatoid arthritis, systemic lupus erythematosus), exposure to elevated burden of pollutants (e.g. particulate matter 2.5, toxic steel pollutants) and erectile dysfunction [9,81,82].

High-sensitivity C-reactive protein

High-sensitivity C-reactive protein (hsCRP) at least 2 mg/l is considered a risk-enhancing factor with greatest utility in those of moderate or intermediate 10-year risk, favouring consideration of statin therapy [10]. hsCRP is particularly useful in that it indicates residual inflammatory risk [83]. One study yielded data suggesting one-third of the participants with established CHD and LDL-C less than 70 mg/dl had serum hsCRP at least 2 mg/l [84]. A patient-level meta-analysis with over 160 000 individuals with no known ASCVD yielded data suggesting adjusted relative risks for incident CHD, ischemic stroke and vascular mortality of 37, 27 and 55%, respectively, for each standard deviation increment in log-normalized hsCRP [85]. A 2020 study yielded data suggesting a reduction in hsCRP by at least 40% was associated with associated with a decreased risk of adverse cardiovascular events in women ($P < 0.0221$) but not in men ($P = 0.2434$) [86].

Recent trials are evaluating the efficacy of anti-inflammatory agents in the targeted approach to lowering CVD risk [87,88]. The Canakinumab Antiinflammatory Thrombosis Outcome Study (CANTOS) demonstrated that canakinumab, an interleukin (IL)-1β inhibitor, was associated with lower rates of recurrent cardiovascular events in those with a prior MI than the placebo group, presumed to be due to greater reduction in hsCRP, notably independent of lipid-level lowering [84]. An ongoing trial, the ZEUS trial, is similarly looking at Ziltivekimab, an IL-6 monoclonal antibody, vs. placebo and the risk of adverse cardiovascular events in those with established ASCVD, CKD, and systemic inflammation [88]. This trial will likely elucidate the role and saliency of anti-inflammatory agents in lowering the increased risk of ACE through targeted approaches to hsCRP and systemic inflammation. With improved ability to treat inflammation, the role of hsCRP as a risk-enhancing factor may become increased in the future.

Family history

CHD in a first-degree relative is an independent risk factor for CVD and demonstrates an additive association with elevated plasma Lp(a) [89]. The ACC/AHA recognize family history of premature ASCVD as a risk-enhancing factor used to enhance risk discrimination derived from the PCE [10]. According to the ACC/AHA Guidelines on the Management of Blood Cholesterol, for those with borderline or

Table 2. Integrated risk tools

IRT	Strengths	Limitations
MESA [16–19]	Expanded risk factor representation; better discrimination in the asymptomatic; better risk discrimination than PCE for borderline risk	Lack of codification in guidelines
PCE-PRS [20,21]	Extended racial/ethnic indications; enhanced predictive performance over the PCE in middle-aged men aged 40–54 years	Lack of codification in guidelines; lack of appraisal of subclinical atherosclerosis
PCE-CAC [7,18,22]	Assessment of subclinical atherosclerosis; effective reclassification of risk in intermediate risk individuals	Lack of codification in guidelines; does not address static, genetic risk, especially, in high-risk groups
CAC-PRS [20,23,24,25▪▪]	Concordance between PRS and CAC	Lack of codification in guidelines; sparse studies
CAC-PCE-PRS	Theoretical: would address subclinical atherosclerosis, traditional risk factors and static genetic risk	No known tools

CAC, coronary artery calcium scoring; MESA, Multiethnic Study of Atherosclerosis Coronary Heart Disease Risk Score; PCE, Pooled Cohort Equations; PRS, polygenic risk scoring.

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intermediate risk according to the PCE, a discussion regarding risk-enhancing factors (e.g. family history) is recommended to adjudicate the decision to initiate moderate intensity statin [12].

DIABETES-SPECIFIC RISK ENHANCERS

Diabetes-specific risk enhancers include at least10-year history of type 2 diabetes mellitus (T2DM), at least 10-year history of type 1 diabetes mellitus (T1DM), at least 30 μg/mg albumin-creatinine ratio, estimated glomerular filtration rate (eGFR) less than 60 ml/min/1.73 m^2, retinopathy, neuropathy and an ankle-brachial index (ABI) less than 0.9 [10]. These risk-enhancing factors should be utilized in the decision to initiate high-intensity statin therapy [10]. However, CAC scoring still works well in these patients, with one study demonstrating significant long-term (i.e. >10 years) prognostication [90]. In a single-centre cohort study of 810 asymptomatic individuals living with T2DM, CAC scoring improved discrimination and reclassification of risk for all-cause mortality greater than risk factors, alone over a study period of 15 years [91]. Another study has yielded data associating increasing CAC scores in patients with T2DM with a greater risk of all-cause mortality, cardiac mortality and incident cardiovascular events [92].

FAMILIAL HYPERCHOLESTEROLEMIA

Familial hypercholesterolemia is less a risk factor than it is a mandate to treat. The saliency of familial hypercholesterolemia as a cardiac risk factor is largely modulated by concurrent serum cholesterol levels. A 2016 study demonstrated that risk of CAD was greater for those with the familial hypercholesterolemia mutation and severe hyperlipidaemia (i.e. LDL-C ≥190 mg/dl) [odds ratio (OR) 22.3, 95% CI 10.7–53.2] than for those with a familial hypercholesterolemia mutation but no severe hyperlipidaemia (OR 6.0, 95% CI 5.2–6.9) when using a reference group of LDL-C less than 130 mg/dl and no familial hypercholesterolemia mutation [93]. Such data suggest a benefit from genetic testing in patients with possible familial hypercholesterolemia, even if only select alleles (e.g. *LDLR*, *APOB*, *PCSK9*), to initiate early LLT, tailor preventive interventions early and provide an opportunity for family-based cascade testing for familial hypercholesterolemia [94]. A study-level meta-analysis demonstrated a prevalence of 45% for CAC = 0 in patients with familial hypercholesterolemia [95]. An additional study looked at 206 individuals with molecularly proven familial hypercholesterolemia and on standard LLT and yielded data suggesting that CAC is the sole marker, which was independently associated with future ASCVD events, and there were no incident ASCVD events in patients with a CAC = 0 over the median 3.7 years of follow up [96]. Therefore LDL-C levels, genetic testing and CAC likely all play a role in risk prediction of the patient with possible or suspected familial hypercholesterolemia.

CURRENT BEST PRACTICE RECOMENDATIONS

Risk stratification should begin with the ACC/AHA-endorsed PCE and identification of risk-enhancing factors, which would further elevate risk, favouring or deemphasizing an indication for initiating statin therapy. For most patients – especially, those of intermediate or borderline risk – this preliminary assessment should be followed up with CAC scoring. If no prior measurement exists, Lp(a) should be measured, as it represents a distinct mechanism of risk not well captured well by traditional tools. However, Lp(a) should generally be measured just once and used to inform the clinician's approach to conceptualizing residual risk after initiation of statin therapy if statin therapy is indicated. If statin therapy is not indicated, Lp(a) should be used as a risk-enhancing factor, with elevated Lp(a) leading the clinician to have a low threshold to initiate LLT. Ultimately, if the patient does not meet criteria or raise clinician suspicion enough to start LLT, the presence of multiple risk enhancing factors should strongly suggest initiation. Routine measurement of advanced lipid tests or hsCRP does not substantial value is not recommended at this time. In the future, as IRT are further developed, validated and formally codified in guidelines, they should be considered as primary tools, as they would comprehensively integrate the risk stratification afforded by tools currently used in a stepwise fashion in the systematic approach to risk stratification (Fig. 2).

FUTURE OF ATHEROSCLEROTIC CARDIOVASCULAR DISEASE RISK ASSESSMENT

The future of ASCVD risk assessment will undoubtably depend upon studies and society guidelines but will largely be shaped by advancements in two areas. First, the further development, optimization and validation of IRT will be a driving force for the future of ASCVD risk assessment. Multiple IRT exist, though none exist with society endorsement [10,12,35]. These IRT will be a 'one stop shop' for conceptualizing and calculation of risk, and may simplify the clinician and patient's understanding of risk assessment. IRT inherently simplify risk

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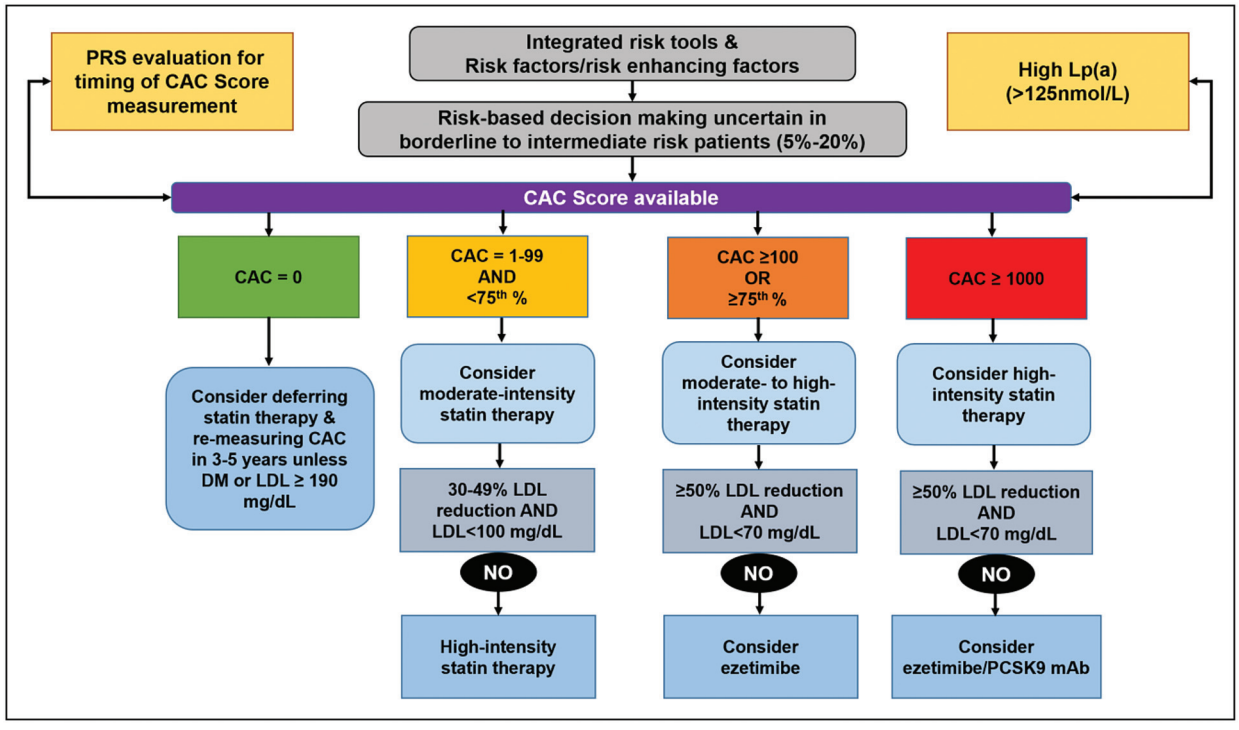
PRS evaluation for timing of CAC Score measurement
Integrated risk tools & Risk factors/risk enhancing factors
Risk-based decision making uncertain in borderline to intermediate risk patients (5%-20%)
High Lp(a) (>125nmol/L)
CAC Score available
CAC = 0
CAC = 1-99 AND <75th %
CAC ≥100 OR ≥75th %
CAC ≥ 1000
Consider deferring statin therapy & re-measuring CAC in 3-5 years unless DM or LDL ≥ 190 mg/dL
Consider moderate-intensity statin therapy
Consider moderate- to high-intensity statin therapy
Consider high-intensity statin therapy
30-49% LDL reduction AND LDL<100 mg/dL
≥50% LDL reduction AND LDL<70 mg/dL
≥50% LDL reduction AND LDL<70 mg/dL
NO
NO
NO
High-intensity statin therapy
Consider ezetimibe
Consider ezetimibe/PCSK9 mAb

FIGURE 2. Current best practice and future recommendations for atherosclerotic cardiovascular risk assessment in patients without an incident adverse cardiovascular event.

assessment by amalgamating multiple risk tools into one. IRT will further improve understanding of risk residual to a particular tool's risk estimation. For example, in a CAC-PCE IRT, what is the risk afforded when there is discordant scoring (e.g. CAC = 0 and high-risk according to PCE or CAC >100 but low risk according to the PCE)?

Second, advancements in determining when to begin CAC scoring will drive future preventive efforts and interventions. Currently, CAC scoring is only indicated in society guidelines for adjudication of benefit from initiating statin therapy when the decision to do so is unclear in patients of intermediate or borderline risk [12]. However, this current schema carries multiple limitations. It mandates the patient's age to be between 40 and 75 years. This precludes those younger than 40 years with unique high risk of ASCVD. In addition, patients must be of borderline or intermediate risk according to the PCE for CAC scoring to be formally indicated, which is commonly not reached in the absence of traditional risk factors. CAC scores increase approximately 25% each year, from the moment CAC more than 0 [97]. Accordingly, it is crucial that CAC be measured prior to being very elevated and, preferably, around the age at which CAC transitions from CAC = 0 to CAC more than 0. Finally, current guidelines rely upon the PCE to reliably predict risk and accurately stratify risk. With limitations in racial/ethnic categories, and a note to interpret results carefully for non-Hispanic African–American and non-Hispanic white adults, the PCE are likely not the ideal basis for determining when to use CAC scoring.

In the future, PRS will, ideally, optimize the decision of when to begin utilizing CAC scoring to stratify and map risk over time. PRS will identify those of particular high risk in early life who may require assessment of subclinical atherosclerosis prior to the age of 40 years, those who may be of low risk according to the PCE but of high risk for early disease progression (i.e. high lifetime risk). Concomitantly, risk factors and risk-enhancing factors will be tracked beginning early in life and the combination of the risk factor and risk enhancing factor burden with PRS will determine when to start CAC scoring. From CAC scoring, treatment can be guided by plaque burden, similar to the plaque profiles used to study the relationship between CAC and progression of atherosclerosis [27▪▪].

CONCLUSION

The PCE, SCORE 2 and SCORE 2-OP are gold-standard traditional risk calculators, but carry important limitations [e.g. limited by their indicated population and design (i.e. population-based tool meant

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for personalization)]. Specific high-risk groups require additional considerations [e.g. MetS, familial hypercholesterolemia, elevated Lp(a)]. CAC imaging enhances risk discrimination, assessing subclinical atherosclerosis, and can be used to adjudicate the initiation of statin therapy or combination LLT and LDL goals in those for whom the decision is unclear, based upon the PCE. Lp(a) is an independent risk factor for premature CHD, serves as the prototypical risk enhancing factor, and therapies are in testing which dramatically lower Lp(a) levels and potentially address Lp(a)'s role in the pathogenesis of ASCVD.

Looking into the future, PRS is a promising risk assessment tool which appraises static risk and will likely have a greater role in future risk assessment tools pertaining to early life risk and projecting lifetime risk. IRT – potentially integrating genetic risk, risk factors, risk-enhancing factors (when present) and subclinical atherosclerosis burden – are a unique opportunity to study discordance between varying risk assessment tools, offering clinicians and physicians a 'one stop shop' for risk calculation, allowing better understanding of what is driving residual risk.

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Conflicts of interest

Earl Goldsborough III BS has no financial disclosures or competing interests to report.

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